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February 1, 2001

Board of Patent Appeals & Interferences
Commissioner of Patents & Trademarks
Washington, D.C. 20231

Re: Julio L. Pimentel
Decreased Fat Absorption with an
Anti-Lipase Antibody
Serial No. 08/888,202
Filed July 7, 1997
Group Art Unit: 1642
Examiner: Susan Ungar

Sir:

Enclosed herewith in triplicate is applicant's brief in the appeal from the final rejection in the above-identified case.

If any additional amounts are required, please charge the cost thereof to our account No. 20-1111.

Respectfully submitted,

John B. Lungmus, Reg. No. 18,566

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IN THE UNITED STATES PATENT & TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Applicant: Julio L. Pimentel	)	
	)	Group Art Unit: 1642
Invention: Decreased Fat Absorption with an Anti-Lipase Antibody	)	Examiner: Susan Ungar
	)	
Serial No. 08/888,202	)	
	)	
Filed July 7, 1997	)	

BRIEF ON APPEAL

(1) Real Party in Interest

XiMed Group PLC, Harwell International Business Centre, Didcot, Oxfordshire, United Kingdom is the owner by assignment of this application and is the real party in interest.

(2) Related Appeals and Interferences

There are no related appeals or interferences.

(3) Status of Claims

This is an appeal from the final rejection of claims 1, 8, 14, 18, 19, 26-28, 31-33, and 37-39, which are all of the claims now remaining in the application.

(4) Status of Amendments

In an amendment filed at the same time as this appeal, applicant cancelled claims 11 and 29 for reasons of redundancy.

(5) Summary of the Invention

This invention is concerned with a method for decreasing the fat absorption in the digestive tract of a post-suckling mammal, particularly a non-ruminant mammal.

The method involves orally administering to such mammal an avian antibody that binds pancreatic lipase in the subject's gastro-intestinal tract, thereby inhibiting the fat-hydrolyzing activity of that enzyme. Dietary fat that would otherwise be broken down and digested, resulting in weight gain (or reduced weight loss), therefore passes through the gastro-intestinal tract and is excreted.

The avian anti-lipase antibody may be fed in water suspension, included in feed as a dry powder, or fed in encapsulated form in liposomes (page 3, lines 15-17; page 6, Example 5; page 7, Example 6). It is prepared by inoculating chickens to produce antibodies specific to lipase and then extracting the yokes of eggs produced by such chickens (page 4, Examples 1 and 2).

An important aspect of this invention lies in the surprising discovery that the method is indeed effective in reducing dietary fat absorption in healthy adult mammals, that is, healthy mammals that have reached at least the post-suckling stage of development. It is well known that antibodies in a mother's milk are capable of traveling through the digestive tract of nursing offspring and of retaining their activity in the not-fully-developed digestive systems of such offspring, but it is also known that gastric acids and enzymes of adult or post-suckling mammals break down proteins as part of the digestive

process, and it would therefore be expected that the activity of an anti-lipase avian antibody would be destroyed or disrupted before reaching the duodenum where pancreatic lipase enters the digestive tract. That such activity is retained in the digestive system of a healthy, adult, non-ruminant mammal is believed to be a surprising discovery that is not disclosed or suggested in the prior art.

This discovery is discussed in the affidavit of August 6, 1999, and supplemental declaration of March 30, 2000, by Dr. Richard Lee Atkinson, Jr. Such affdavit and declaration were submitted for the Examiner's consideration during prosecution of this application and, for the convenience of the Board, are also included here as Appendices B and C. Dr. Atkinson, who has no financial interest in this invention, is a foremost authority on nutritional medicine, is currently Professor of Medicine and Nutritional Sciences, and Director at the Beers-Murphy Clinical Nutrition Center, at the University of Wisconsin, and has received numerous titles and honors in connection with his work in clinical nutrition and treatment of obesity, all as revealed by the Curriculum Vitae appended to his affidavit (App. B).

(6) <u>The Rejection and Applied References</u>

In the final action of June 29, 2000 (Paper 17), the Examiner relied upon a single primary reference (Hadvary

et al 4,598,089) and combined it with a total of nine secondary references to support a rejection of the claims on appeal for obviousness under 35 USC Section 103. The references are as follows:

Hadvary et al	4,598,089
Tokoro	5,080,895
Coleman	5,585,098
Sterling et al	5,753,228
Japan (Kajita et al)	02150294

Moloney, Livestock Production Science, 1995, 42:239-245

Flint, Proceedings of the Nutrition Society, 1992, 51:433-439

Ohkaru et al, Clin. Chim. Acta, 1989, 182:295-300

Perryman et al, Infection and Immunity, 1993, 61:4906-4908

Martin et al, Am. J. Physiol., 1994-266:G417-G424

It should be noted that Ohkaru et al and Japanese patent 02150294 were treated by the Examiner as alternative references directed to similar immunoassays.

The precise status of three of the above as being applied references is somewhat in doubt because in the final action, and in earlier actions (Papers 5, 8 and 13) cross-referenced in the final action, Sterling et al, Perryman et al, and Martin et al were not specifically listed as secondary references in the opening sentences of the paragraphs dealing with Section 103 rejection.

However, in Section 3 of the final action, the Examiner states that the claims stand rejected for the reasons given in earlier actions, among which is specified Paper 13, Section 5, pages 2-5, and in the text of that earlier action (on page 4), reliance was indeed placed on these three references. In addition, the same three references are included in the discussion on page 3 of the final action.

(7) Grouping of Claims

With regard to the rejection on obviousness, it is believed that all of the claims on appeal fall into the same group.

(8) Issues

As to the rejection of all of applicant's claims for obviousness under 35 USC 103, the issues are:

(a) Whether the Examiner properly determined that there is something in the prior art that would motivate or suggest to one of ordinary skill in the art to do what applicant has claimed;

(b) Whether the Examiner made out a prima facie case of obviousness and, if so, whether it has been rebutted by applicant;

(c) Whether proper weight was given by the Examiner to the affidavit and supplemental declaration by Dr. Atkinson.

(9) Argument

(a) There is nothing in the references that would motivate or suggest to one skilled in the art to combine them in the manner indicated by the Examiner, and therefore the combination of references is not a proper one.

It is applicant's position that the references are from diverse and in some cases non-analogous fields, and that the only motivation for combining them as the Examiner has done is applicant's own disclosure. Absent some suggestion or motivation gleaned from the references themselves, such hindsight analysis is clearly improper.

Statements by the Federal Circuit in In re Oetiker, 24 USPQ2d 1445-1446 (1992) are believed particularly pertinent here:

> "In order to rely on a reference as a basis for rejection of the applicant's invention, the reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the inventor was concerned. (citing cases) * * *
>
> The combination of elements from non-analogous sources, in a manner that reconstructs the applicant's invention only with the benefit of hindsight, is insufficient to present a prima facie case of obviousness. There must be some reason, suggestion, or motivation found in the prior art whereby a person of ordinary skill in the field of the invention would make the combination. That knowledge cannot come from the applicant's invention itself. (citing cases)
>
> * * *
>
> We conclude that the references on which the Board relied were improperly combined."

A similar improper combination of references is believed to have occurred here. Applicant does not dispute that the primary Hadvary et al reference is in the same field of nutrition and obesity control. The Hadvary et al reference is the only one cited by the Examiner dealing

with the oral administration of a lipase blocking agent, namely, tetrahydrolipstatin (trade name: Xenical). While tetrahydrolipstatin, a leucine derivative produced from streptomyces strains found in the soil, is active against pancreatic lipase in animals, such a compound does not have the same mode of action as anti-lipase antibodies. Applicant's invention works via an antigen-antibody reaction, whereas the compounds of the reference do not participate in such a reaction and are not systemically absorbed. In short, tetrahydrolipstatin is an entirely different molecule unrelated to antibodies of any sort.

Applicant understands the Examiner's position to be that while tetrahydrolipstatin is indeed a different substance, the secondary references would suggest to an artisan that avian lipase antibodies might be substituted for tetrahydrolipstatin and that results similar to those disclosed and claimed by applicant might be achieved. The secondary references carry no such suggestion, however, and applicant is unaware of any prior art that might be considered as making such a suggestion either prior to Hadvary et al or in the 14 years since the Hadvary et al patent issued.

Applicant submits that the Examiner erred in determining that one of skill in the art would have been motivated to select and combine these references in a

manner that renders the claimed invention obvious. While much is known and volumes have been written about antibodies, their production and physiological effects, it is not seen that the Examiner has identified any motivation for choosing the secondary references for combination. None, that is, except applicant's own disclosure used as a blueprint for piecing together such diverse references in an effort to make out a prima facie case of obviousness.

As stated by the Federal Circuit in In re Rouffet, 47 USPQ2d 1453, 1457-58 (1998):

> "If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention. Such an approach would be 'an illogical and inappropriate process by which to determine patentability.' Sensonics, Inc. v. Aerosonic Corp., 81 F.3d 1566, 1570, 38 USPQ2d 1551, 1554 (Fed. Cir. 1996).
>
> To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed."

Applicant understands the Examiner's position to be

that if an artisan were concerned with the treatment of obesity, he might look to the teachings of Moloney and Flint. However, the Moloney and Flint references are primarily concerned with using cytotoxic antibodies, administered intravenously or subcutaneously (not orally) to rupture and thereby destroy existing fat cells or adipocytes. Such teachings differ markedly from applicant's method in terms of the antibodies involved, the way they are administered, and the actions and results produced, but the Examiner indicates that an artisan might then consider substituting pancreatic lipase antibodies as disclosed by Ohkaru et al and JP 02150294 (Kajita et al). As to oral administration, the Examiner then adds Tokoro, Coleman, Sterling, Perryman et al and Martin et al.

What is believed apparent from this collection of references is that any motivation or suggestion for bringing them together cannot be found in the references themselves but rather in applicant's own disclosure. For example, while it is true that Ohkaru et al and JP 02150294 discuss the use of monoclonal pancreatic lipase antibodies, these references relate to the field of clinical pathology and are concerned with laboratory procedures, not with obesity or nutrition. These references describe the use of pancreatic lipase antibodies in clinical assays for the measurement of lipase that has leaked into the bloodstream

from cells damaged from pancreatitis. Nothing in these references provides a suggestion or motivation for combining them with other secondary references, and with Hadvary et al, to piece together the method called for in applicant's claims.

The oral administration of various antibodies is well known in the art, but the other secondary references also fail to provide any motivation or suggestion for combining them with the references discussed above. Tokoro is directed to the treatment of infectious diseases in neonatal mammals caused by a pathogenic organism that has not acquired resistance to a specific antibody-containing substance. Coleman is directed to the treatment of diseases in lactating ruminant animals, and Perryman et al and Sterling et al deal with the oral administration of parasite-reducing antibodies in treating intestinal parasitosis caused by C. parvum. Martin et al discloses oral administration of monoclonal antibodies to mammals in the suckling period of development to stimulate gastrin cell activity. While these references all relate to antibodies and oral administration, it is submitted that they lack any teaching, suggestion, or motivation for combining them with the other secondary references and the primary reference to support a determination of obviousness with respect to applicant's claimed invention.

It is therefore submitted that, in view of the above, the Examiner has failed to make out a prima facie case for obviousness under Section 103.

(b) Even if the references were combinable, the teachings of all of them taken together fail to suggest that lipase antibodies would remain active to inhibit fat absorption in the digestive tract of a healthy post-suckling mammal.

Assuming for sake of argument that all 10 references are properly combinable, it is believed that their combined teachings still fall far short of rendering the claimed invention obvious within the meaning of Section 103. Simply stated, none of the references discloses the oral administration of antibodies -- much less pancreatic lipase antibodies -- to control a normal digestive function in a healthy adult (or at least post-suckling) mammal, and it is therefore submitted that all of the references taken in combination fall short of that teaching.

Applicant's claims specifically require a mammalian subject to be in the "post-suckling" stage of development. As discussed in Section 5 of this brief, and as stated in Dr. Atkinson's affidavit and supplemental declaration, antibodies in a mother's milk are capable of traveling through the digestive tract of nursing offspring and of retaining their activity because the digestive systems are not sufficiently developed. As the offspring matures,

its digestive system advances in its ability to digest protein and, once the young mammal has passed the suckling stage, and assuming its digestive system has no abnormalities and is free of disease, it would be expected that orally administered lipase antibodies would not reach the lower intestine without being broken down by the digestive process itself.

In an amendment filed April 14, 2000 (Paper 16), applicant noted that one skilled in the art might contemplate the possibility that different types of antibodies, such as those capable of attacking disease-causing organisms, might be administered to an adult mammalian subject and not be broken in the digestive tract if the pathological condition were such that the digestive process had been rendered partially or wholly inoperative. The method of this invention is not concerned with treatment of such a pathological condition, however; it assumes that the mammalian subject has reached an advanced stage in the development of its digestive tract and that the digestive process is normal and not disrupted.

None of the references discloses the oral administration of antibodies of any type (much less pancreatic lipase antibodies) to control a normal digestive function in a healthy post-suckling mammal. The primary Hadvary et al reference does not deal with antibodies at

all, and Moloney, Flint, Ohkaru et al and JP 02150294 (Kajita et al) all relate to procedures in which antibodies are introduced intravenously, subcutaneously, or intraperitoneally, not orally. Coleman is concerned with a special case of ruminants, and Tokoro and Martin et al deal specifically with very young (i.e., suckling) mammals whose digestive tracts are in early stages of development. While Perryman et al and Sterling et al refer to adult subjects (although all of the examples in Sterling et al involve only newborn mammals), both references are concerned with the treatment of subjects with parasite-reducing antibodies to treat intestinal infections (from C. parvum) which disrupt normal operations of the animals' digestive systems. While a skilled artisan reading these patents could conclude that parasite-reducing antibodies survive the digestive tract of a mammal whose digestive process is disrupted because of intestinal parasitosis, that does not make it obvious that different antibodies having a specificity for a normally-produced enzyme would be able to pass through the digestive tract of a healthy adult mammal and still retain enzyme-inhibiting binding capabilities.

Therefore, even if all 10 references could be considered properly combinable, their teachings taken as a whole fail to disclose the oral administration of antibodies, and specifically pancreatic lipase antibodies,

to control a normal digestive function in a healthy post-suckling non-rumminant mammal. In the absence of such a disclosure that might be gleaned from the combined teachings of all of the references taken together, it is submitted that the Examiner has failed to make out a prima facie case for rejecting applicant's claims for obviousness under Section 103.

Applicant would like to add here a comment concerning the Sterling et al reference that was made during prosecution of the application. That reference is believed to constitute a good illustration of non-predictability and non-obviousness in the treatment of one condition in relation to the treatment of another. Sterling et al are concerned with the treatment of one type of infection, a parasitic infection, by developing passive immunity, but they cite numerous references that teach that other types of infections, at least in newborns, may also be treated by administering specific egg yoke antibodies. The Sterling et al method was nevertheless considered to be unobvious and patentable over the recognized prior art. In the present situation, the differences are far more striking because applicant is not dealing with the prevention or treatment of infection or invasion by foreign organisms. Applicant is instead inactivating a natural enzyme, pancreatic lipase, and doing so with antibodies that would

not be expected to remain intact in the digestive tract of an adult (post-suckling) non-ruminant mammal.

(c) The Examiner failed to give proper weight to the affidavit and supplemental declaration by Dr. Akinson.

In his Affidavit and Supplemental Declaration, Dr. Atkinson states that prior to reading the specification and claims of this application, he was "skeptical that antibodies introduced into the small intestine, i.e., into the gastro-intestinal tract, in humans and other non-ruminant mammals, would have any activity past the newborn period." (Affidavit, par. 15) His skepticism "was due in part to the fact that the large amount of gastric acid and protein digestive enzymes in the human digestive system would be expected to destroy any [pancreatic lipase] antibodies before they could reach the point in the duodenum where pancreatic lipase enters." (Affidavit, par. 17) He then states that it was therefore not obvious to him that antibodies could reach the duodenum and still be active to inhibit pancreatic lipase. (Affidavit, par. 20)

Section 103 refers to what should be considered obvious to a person having "ordinary skill in the art to which said subject matter pertains," and it can be fairly observed that Dr. Atkinson is well beyond the level of someone of ordinary skill in the fields of nutrition and obesity treatment. Two further observations are believed

appropriate, however. One is that something unobvious to one of extraordinary skill in the art could also be expected to be unobvious to one of lesser skill. The second is that one does not have to be a medical expert to know that proteins, including antibodies, would be expected to be broken down in the digestive systems of healthy adult mammals.

Statements to that effect can be found in any of a variety of basic and advanced texts, of which the following is simply one example:

> **DIGESTION IN THE STOMACH. There are only two known enzymes produced in the stomach, pepsin and rennin. Pepsin is secreted in the inactive form pepsinogen and activated by hydrochloric acid. Once pepsin is formed it is capable of activating more pepsinogen. Pepsin belongs to a group of protein digesting enzymes called endopeptidases (which include the enzymes trypsin and chymotrypsin produced by the pancreas). These enzymes by acting upon the peptide bonds (p. 104) within the molecules of protein break up the large protein molecules into smaller fragments. These smaller fragments are then further broken down by a group of enzymes, produced by the small intestine, called exopeptidases. These exopeptidases act by breaking down terminal peptide bonds to liberate free amino acids. The differences between pepsin, trypsin and chymotrypsin lie in the fact that each enzyme is capable of breaking down only certain peptide bonds, depending upon the chemistry of the protein molecule adjacent to the peptide bond.**
>
> **In the stomach then, protein digestion is begun by the action of pepsin, which, by acting as an endo-peptidase, breaks down the molecules of protein into smaller fragments. The smaller fragments, sometimes called polypeptides, are broken down further when they pass into the duodenum and small intestine and meet other enzymes.**

P.C. and A.G. Clegg, Biology of the Mammal, pp. 386-387 (4th Ed., Heinemann, 1975)*

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* Copies of the relevant pages of this text are appended hereto as Appendix D.

In view of the above, it is believed that the Examiner failed to give proper weight to the statements made by Dr. Atkinson, particularly with respect to his skepticism and the reasons for it. In the final action, the Examiner observed (pages 2-3):

> "In the Atkinson Declaration, Dr. Atkinson argues that (a) he would have been skeptical that lipase antibodies induced orally into the GI tract of post-newborn non-ruminant mammals would have any significant effect in inhibiting pancreatic lipase activity and the teachings of the references, taken in combination would not have led him to a different conclusion .... The arguments have been considered but have not been found persuasive (a') as previously stated, it was conventional in the art at the time the invention was made, to orally administer antibodies to animals for intestinal treatments. The stated opinion of Dr. Atkinson, relating specifically to his skeptism that the anti-lipase antibody would remain active upon oral administration is not persuasive in view of the multiple references presented that specifically demonstrate that orally administered antibodies retain activity in the gastro intestinal tract...."

The "multiple references" are not specifically identified in this quotation but, in the discussion on page 3, mention is made of Tokoro, Martin et al, Perryman et al and Sterling et al.

These references were discussed by applicant at some length in the amendment (Paper 16) preceding the final action and also by Dr. Atkinson in his Supplemental Declaration. As noted by Dr. Atkinson, Perryman et al and Sterling et al do refer to the treatment of adult mammals but in those cases the mammals have their digestive

processes disrupted by intestinal parasitosis. While a skilled artisan reading Perryman et al and Sterling et al could conclude that parasite-reducing antibodies might survive the digestive tract of a mammal whose digestive process is disrupted because of intestinal parasitosis, that does not make it obvious that entirely different antibodies having a specificity for a normally-produced enzyme would be able to pass through the digestive tract of a healthy adult mammal and still retain enzyme-inhibiting binding capabilities.

Also, while the Sterling et al specification mentions that adult subjects might be treated, the only examples given in the patent deal with the treatment of newborn mammals (mice). There are no data in the patent to support the assertion that the Sterling et al method would be effective treatment for adults as well as newborns. There is a vast difference between the two, and applicant's claimed invention is concerned only with the treatment of post-suckling mammals.

Like Sterling et al, the Martin et al reference is specifically concerned with the oral administration of antibodies to mammals in the suckling period of post-natal development. As noted by Dr. Atkinson in his Supplemental Declaration, it is not surprising that such antibodies retain activity in such young mammalian subjects, but the

Martin et al reference is not concerned with the treatment of older mammals and cetainly does not indicate or suggest that lipase antibodies would retain their effectiveness if orally administered to healthy post-suckling mammals.

Therefore, of the "multiple references" alluded to by the Examiner as demonstrating that orally administered antibodies retain activity in the gastro intestinal tract, that leaves only Tokoro. As acknowledged by the Examiner on page 4 of the final action, Tokoro specifically teaches the oral administration of antibodies to suckling mammals, and it might also be noted that the claims of the Tokoro patent are specifically limited to a method "for preventing or treating an intestinal infectious disease in a neonatal mammal caused by a pathogenic organism." The only example of treatment given in Tokoro concerns the treatment of newborn pigs challenged by the antigen ETEC which is known to cause diarrhea. Despite the fact that the Tokoro method is concerned specifically with newborn mammals having intestinal infectious diseases, the Examiner, noting that elsewhere in the Tokoro specification there is language suggesting that the method might include treatment not limited to newborn or suckling mammals, concludes that one skilled in the art and familiar with the Tokoro reference would consider applicant's claimed method obvious within the meaning of Section 103.

Dr. Atkinson, as one who is very clearly skilled in the art, is of a different view, and his Affidavit and Supplemental Declaration give reasons why applicant's claimed invention should be considered unobvious over the teachings of the references. He explains the reasons for his skepticism that applicant's anti-lipase antibody would remain active upon oral administration to a healthy post-suckling mammal, and it is submitted that such testimony is entitled to considerable weight and refutes and effectively rebuts what the Examiner regards to be a prima facie case of obviousness.

The case of In re Dow Chemical Co., 5 USPQ2d 1529, 1532 (1988) is believed relevant here because the claims were directed to a chemical invention by Dow employees which the PTO had rejected as obvious despite statements from one of Dow's expert polymer scientists (Dr. Keskula) that he had been skeptical about the invention and was personally surprised that it worked. The PTO argued that at least it would have been obvious to try doing what applicant had done. That argument was rejected, and the Board's decision was reversed, with the following statements:

> "The PTO presents, in essence, an 'obvious to experiment' standard for obviousness. However, selective hindsight is no more applicable to the design of experiments than it is to the combination of prior teachings. There must be reason or suggestion in the art for selecting the procedure used, other than the knowledge learned from the

applicant's disclosure (citing cases). Of the many scientific publications cited by both Dow and the PTO, none suggests that any process could be used successfully in this three-component system to produce this product having the desired properties. The skepticism of an expert, expressed before these inventors proved him wrong, is entitled to fair evidentiary weight (citing cases) as are the five to six years of research that preceded the claimed invention. The evidence as a whole does not support the PTO's conclusion that the claimed invention would have been obvious in terms of 35 USC §103." (emphasis supplied)

Earlier in the same opinion, the Court also noted (5 USPQ2d at 1531):

"The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art. (citing cases) Both the suggestion and the expectation of success must be founded in the prior art and not in the applicant's disclosure."

(10) Conclusion

Taking together all of the multiple references cited by the Examiner to support the rejection of applicant's claims, applicant submits that the combination still falls far short of rendering that invention obvious to one skilled in the art. The skepticism expressed by Dr. Atkinson, and the reasons given for that skepticism, are believed significant here. While applicant would not agree that the combined references make out a prima facie

case for rejection of the claims as they are now presented on appeal, it is submitted that in any event the grounds for rejection have been effectively rebutted by Dr. Atkinson's statements and the facts and arguments set forth herein.

Accordingly, it is respectfully requested that the final rejection of applicant's claims under Section 103 be reversed. Applicant submits this brief in triplicate, along with a check in the amount of $155.00.

Respectfully submitted,

John B. Lungmus Reg. No. 18,566

TILTON, FALLON, LUNGMUS & CHESTNUT
100 South Wacker Drive
Chicago, Illinois 60606
A/C 312/456-8000

Dated: 2/1/01

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patent and Trademarks, Washington D. C. 20231 on 2/1/01
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CLW6465
Name of applicant assignee, or Registered Representative
Signature
2/1/01
Date of Signature

(11) Appendix A

1. A method for inhibiting pancreatic lipase so as to reduce fat absorption in a post-suckling mammal by orally feeding said mammal an avian antibody that binds pancreatic lipase in the gastro-intestinal tract of said mammal to inhibit the fat-hydrolyzing activity of said pancreatic lipase.

8. The method of claim 1 wherein said mammal is a non-ruminant and wherein prior to the step of feeding said mammal said avian antibody, said antibody is produced in avian eggs.

14. The method of claim 1 wherein prior to the step of feeding said avian antibody, the antibody is first freeze dried.

18. The method of claim 1 wherein the orally fed antibody is fed in powder form.

19. The method of claim 18 wherein the powder antibody is fed as part of a processed or prepared food.

26. The method of claim 8 wherein the antibodies are obtained from the yolk of an egg without fractionation thereof.

27. The method of claim 8 wherein the antibody is obtained by fractionating the egg yolk resulting in a protein concentrate of pure chicken immunoglobulin.

28. The method of claim 1 wherein prior to the step of feeding said avian antibody, the antibody is first spray dried.

31. The method of claim 1 wherein the orally fed antibody is fed in a liquid form.

32. The method of claim 1 wherein the orally fed antibody is fed in a compressed tablet form.

33. The method of claim 1 wherein prior to the step of feeding said avian antibody, the antibody is first processed by encapsulation to cause said antibody to be protected against entities, processes or changes which might otherwise cause said antibody to be inactivated, reduced in effectiveness or disrupted.

37. The method of claim 39 wherein said antibody is introduced into the digestive system of the non-ruminant mammal by orally feeding said antibody to the non-ruminant mammal in a capsule that protects said antibody until the antibody reaches said lower gastro-intestinal tract.

38. A method of altering the normal digestive process of a post-suckling mammal to inhibit the absorption of fat, comprising the steps of immunizing a producer animal with pancreatic lipase to produce pancreatic lipase antibody, and then orally administering said antibody to said post-suckling mammal to bind pancreatic lipase in its gastro-intestinal tract and thereby inhibit the fat-hydrolyzing activity of said pancreatic lipase in said tract.

39. The method of claim 38 in which said post-suckling mammal is a non-ruminant.

APPENDIX B

PATENT
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Julio L. Pimentel	)	
		)	Examiner: Ungar
Serial No.:	08/888,202	)	
		)	Art Unit: 1642
Filed:	July 7, 1997	)	
		)	
For:	DECREASED FAT ABSORPTION WITH ANTI-LIPASE ANTIBODY	)	

AFFIDAVIT UNDER 37 C.F.R. § 1.132

Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231

I, Richard Lee Atkinson, Jr., M.D., do hereby declare as follows:

1. I am Chief of the Section of Clinical Nutrition and Director of the Beers-Murphy Clinical Nutrition Center at the University of Wisconsin at Madison. I am a practicing clinical nutritionist.

2. My curriculum vitae is attached hereto as Exhibit A.

3. I am co-founder and President of the American Obesity Association, a non-profit organization, which pursues better quality of life for individuals with obesity and government recognition of obesity as a disease.

4. I am a former President of the North American Association for the Study of Obesity, an organization comprised of researchers, scientists, academicians, and clinicians who

share a common purpose to advance obesity research.

5. I am a former President of the American Society of Clinical Nutrition, an organization comprised of researchers, scientists, academicians, and clinicians who share a common purpose to advance research and education in clinical nutrition.

6. I have read and am familiar with the specification, including the claims, of U.S. Patent Application No. 08/888,202, filed July 7, 1997, by Julio L. Pimentel, entitled Decreased Fat Absorption With an Anti-Lipase Antibody.

7. Prior to being approached to review the specification, including the claims, of U.S. Patent Application No. 08/888,202, in connection with the preparation of this Affidavit, I had no dealings with the inventor, Julio L. Pimentel, with the assignee, XiMed Group PLC, or any of its predecessors in interest or legal representatives.

8. Obesity is a worldwide health problem that has reached epidemic proportions in the United States and globally according to the World Health Organization (WHO) [Reference: Preventing and managing the global epidemic of obesity: report of a WHO Consultation on Obesity. Geneva, 3-5 June, 1997. WHO/NUT/NCD98.1, Geneva, 1998.]

9. Obesity is predicted by reports of the United States Government and the WHO to increase dramatically the cost of health care in the United States and to seriously deplete healthcare budgets for underdeveloped countries by early in the 21st century. [References: 1) Preventing and managing the global epidemic of obesity: report of a WHO Consultation on Obesity. Geneva, 3-5 June, 1997. WHO/NUT/NCD98.1, Geneva, 1998., 2) Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults - The Evidence Report. Obesity Research 6(Suppl 2):51S-209S, 1998.]

10. Obesity was identified as a serious health concern by Aristotle and by physicians and scientists ever since then.

11. Obesity is a cause or major contributing factor to many life threatening human illnesses or conditions, including diabetes mellitus, hypertension, dyslipidemia, atherosclerosis, cardiac disease, cerebrovascular accidents, sleep apnea, gallbladder disease, cancer, and gout, among others.

12. According to the National Academy of Sciences, obesity is the second leading cause of preventable deaths in the United States. [Reference: Thomas PR, ed. 1995. Weighing the Options. Criteria for Evaluating Weight-Management Programs. Washington: National Academy Press.]

13. Many drugs that were developed and marketed have not been successful or have caused undesirable side effects and have been removed from the market, or their use abandoned by physicians, including such drugs as chlorphentermine, dexamphetamine, dexfenfluramine, fenfluramine, Mazinor^{R}, methamphetamine, and phenmetrazine. [Reference: Atkinson RL. Use of drugs in the treatment of obesity. Annual Review of Nutrition 17:383-403, 1997.]

14. An effective method of reducing obesity would be to inhibit pancreatic lipase in the gastro-intestinal tract, thus leading to the malabsorption of a portion of dietary fat.

15. Prior to reading the specification, including the claims, of U.S. Patent Application No. 08/888,202, I was skeptical that antibodies introduced into the small intestine, i.e. into the gastro-intestinal tract, in humans and other non-ruminant mammals, would have any activity past the newborn period.

17. My skepticism as to the possibility of introducing antibodies into the gastro-intestinal tract in post-newborn humans and other non-ruminant mammals for the purpose of inhibiting pancreatic lipase was due in part to the fact that the large amount of gastric acid and protein digestive enzymes in the human digestive system would be expected to destroy any

antibodies before they could reach the point in the duodenum where pancreatic lipase enters.

18. The claimed invention of U.S. Patent Application No. 08/888,202 requires the antibodies to reach the duodenum of the gastro-intestinal tract (GI tract) and still be active to inhibit pancreatic lipase.

19. One of the types of lipase it is desirable to inhibit, in order to assist in combating obesity, is pancreatic lipase, the enzyme responsible for digestion of most of the fat in the human GI tract.

20. That antibodies can reach the duodenum and still be active to inhibit pancreatic lipase was not obvious to me as of July 7, 1997.

21. Although initial positive pancreatic lipase blocking results have been achieved using tetrahydrolipstatin (generic name: orlistat, trade name: Xenical^{R}), which is not systemically absorbed, Xenical^{R} is an entirely different molecule that is unrelated to human or animal antibodies. Also, it is possible that individuals might become allergic to Xenical^{R}, which would prevent its use in certain groups of prospective obese patients. [Reference: 1) Package insert, Xenical^{R}, Hoffman-LaRoche, Inc., 2) James WP, Avenell A, Broom J, Whitehead J. A one year trial

to assess the value of orlistat in the management of obesity. Int J Obesity 21(Suppl 3):S24-S30, 1997.]

22. Because of the possibility that allergenicity might prevent the use of Xenical^{R} in certain groups of prospective obese patients, it is my opinion that there remains a need for alternate methods of inhibiting pancreatic lipase in the gastro-intestinal tract, and this need has not been satisfied by Xenical^{R}.

22. I have reviewed the Office Actions mailed August 18, 1998 and February 3, 1999, and have read each of the references cited by the Examiner.

23. In my opinion, based on the teachings of the references cited in the Examiner's rejections under 35 U.S.C. § 103 in the Office Actions mailed August 18, 1998 and February 3, 1999, namely item number 9 of the August 18, 1998 Office Action and item numbers 5, 7 and 8 of the February 3, 1999 Office Action, the references do not render the claimed invention obvious because the references relate to non-analogous art from one another and would not be combined in the manner proposed by the Examiner.

24. In my opinion, based on the teachings of the references cited in the Examiner's rejections under 35 U.S.C. § 103 in the

Office Actions mailed August 18, 1998 and February 3, 1999, namely item number 9 of the August 18, 1998 Office Action and item numbers 5, 7 and 8 of the February 3, 1999 Office Action, the references do not render the claimed invention obvious because the references relate to non-analogous art from the claimed invention and therefore would not be looked to by those skilled in the art seeking to solve the problem of inhibiting lipase in the gastro-intestinal tract.

25. Based upon my review of the Hadvary et al. patent, U.S. Patent No. 4,598,089, it is my opinion that the Hadvary patent is in the biochemistry art, it does not concern antibodies, and the patent only shows one very different treatment for obesity than the method claimed in U.S. Patent Application No. 08/888,202.

26. Based upon my review of the Ohkaru et al. reference, (Clin. Chim. Acta (1989) 182:295-300), it is my opinion that the Ohkaru et al. reference is in the art of clinical pathology, which is an art non-analogous to the biochemistry art of the Hadvary et al. patent, and because the Ohkaru et al. reference is in clinical pathology, as opposed to biochemistry, one would not look to Ohkaru et al., either alone or in combination with the other references cited by the Examiner, to modify or add to Hadvary et al., U.S. Patent No. 4,598,089, to arrive at the method claimed in U.S. Patent Application No. 08/888,202.

27. Based upon my review of the Ohkaru et al. reference, it is my opinion that the Ohkaru et al. reference relates to the use of monoclonal antibodies against pancreatic lipase that enabled development of a clinical assay for the measurement of pancreatic lipase that had leaked into the bloodstream from damaged cells in individuals with pancreatitis, which is not analogous to the art of the claims of U.S. Patent Application No. 08/888,202, which require the delivery of antibodies through the digestive system and into the gastro-intestinal tract to inhibit lipase.

28. Based upon my review of the Kajita et al. reference, JP 02150294, it is my opinion that the Kajita et al. reference is in the art of clinical pathology, which is an art non-analogous to the biochemistry art of the Hadvary et al. patent, and because the Kajita et al. reference is in clinical pathology, as opposed to biochemistry, one would not look to the Kajita et al. reference, either alone or in combination with the other references cited by the examiner, to modify or add to Hadvary et al., U.S. Patent No. 4,598,089, to arrive at the method claimed in U.S. Patent Application No. 08/888,202.

29. Based upon my review of the Kajita et al. reference, it is my opinion that the Kajita et al. reference does not discuss obesity or nutrition, but instead relates to the use of monoclonal antibodies directed against pancreatic lipase that enabled development of a clinical assay for the diagnosis of the

presence of pancreatic lipase in the bloodstream in individuals with pancreatitis, and the Kajita et al. is not analogous to the art of the claims of U.S. Patent Application No. 08/888,202, which require the delivery of antibodies through the digestive system and into the gastro-intestinal tract to inhibit lipase.

30. Based upon my review of the Moloney reference (Livestock Production Science, 1995, 42:239-245), it is my opinion that the Moloney reference is directed to the unrelated problem of making antibodies to insulin and injecting antibodies into the blood stream, and the Moloney reference would not be looked to by one trying to solve the problem solved by the claims of U.S. Patent Application No. 08/888,202, which require the oral delivery of antibodies through the digestive system and into the gastro-intestinal tract to inhibit lipase. These are fundamentally different because antibodies injected into the bloodstream would not be immediately destroyed, whereas I would have expected that antibodies taken by mouth would be immediately destroyed in the stomach or upper duodenum. In addition, since Moloney is directed to those interested in destroying fat cells, as opposed to inhibiting pancreatic lipase, thus one would not be motivated to look to the Moloney reference, either alone or in combination with the other references cited by the examiner, to modify or add to Hadvary et al., U.S. Patent No. 4,598,089, to arrive at the method claimed in U.S. Patent Application No. 08/888,202.

31. Based upon my review of the Flint reference, Proceedings of the Nutrition Society, 1992, 51:433-439), it is my opinion that the Flint reference is directed to the unrelated problem of destroying fat cells with antibodies by injecting the antibodies into humans in order to cause the fat cells to rupture and release all the fat they contain. This theoretical treatment, in my opinion, is entirely unrelated and non-analogous to the use of antibodies against pancreatic lipase, and the Flint reference would not be looked to by one trying to solve the problem solved by the claims of U.S. Patent Application No. 08/888,202, which require the oral delivery of antibodies through the digestive system and into the gastro-intestinal tract to inhibit lipase. Furthermore, one would not look to the Flint reference, either alone or in combination with the other references cited by the examiner, to modify or add to Hadvary et al., U.S. Patent No. 4,598,089, to arrive at the method claimed in U.S. Patent Application No. 08/888,202.

32. Based upon my review of the Coleman patent, U.S. Patent No. 5,585,098, this patent is totally unrelated to treating obesity, but rather, is concerned with treating a disease in ruminant animals, specifically to the use of antibodies against some of the pathogens that cause mastitis in cattle. This is not analogous to the use of antibodies against pancreatic lipase in the gastro-intestinal tract of non-ruminant mammals. One would not look to the Coleman patent, either alone or in combination

with the other references cited by the examiner, to modify or add to Hadvary et al., U.S. Patent No. 4,598,089, to arrive at the method claimed in U.S. Patent Application No. 08/888,202.

33. Based upon my review of the Tokoro reference, U.S. Patent No. 5,080,895, it is my opinion that this patent is totally unrelated to treating obesity, but rather, is concerned with preventing or treating an intestinal infectious disease in a neonatal mammal caused by a pathogenic organism which has not acquired resistance to a specific antibody containing substance. This is not analogous to the use of antibodies against pancreatic lipase in the gastrointestinal tract. Further, one would not look to the Tokoro patent, either alone or in combination with the other references cited by the Examiner (such as the Kajita et al. reference, JP 02150294, which in my opinion is in the art of clinical pathology, an art non-analogous to the biochemistry art of the Hadvary et al. patent) to modify or add to the Hadvary et al. reference to arrive at the method claimed in U.S. Patent Application No. 08/888,202.

34. Based upon my review of the Murase et al. reference, Atherosclerosis, 1981, 39:293-300), it is my opinion that the Murase et al. reference is in the art of clinical pathology, which is an art non-analogous to the biochemistry art of the Hadvary et al patent. Specifically, Murase et al. relates to the use, by injection into the jugular vein of rats, of an antibody

prepared specifically against the enzyme hepatic lipase in order to investigate the role of this enzyme in lipoprotein metabolism. One searching for an obesity treatment would not turn to Murase et al. to find any suggestion as to a solution involving the oral introduction of anti-lipase antibodies into non-ruminant mammals, even if that person were aware of the other references cited by the Examiner. As such, one would not look to the Murase et al. reference, either alone or in combination with the other references cited by the Examiner, to modify or add to Hadvary et al. to arrive at the method claimed in U.S. Patent Application No. 08/888,202.

I affirm that the statements above are true to the best of my knowledge and belief, and I am aware that any false statements herein may subject me to penalties for perjury and may jeopardize the validity of any patent or patents that may issue on the subject patent application.

Dated: August 6, 1999

Richard L. Atkinson, Jr.

Richard Lee Atkinson, Jr., M.D.

Signed before me this 6th day of August, 1999.

John L. Steinick

Notary Public

February, 1999

CURRICULUM VITAE

RICHARD LEE ATKINSON, JR., M.D.

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PROFESSIONAL APPOINTMENTS:

Professor of Medicine and Nutritional Sciences; Director, Beers-Murphy Clinical Nutrition Center; Chief, Section of Clinical Nutrition; University of Wisconsin; 1993 - Present

Professor of Internal Medicine; Chief, Division of Clinical Nutrition; Eastern Virginia Medical School; Norfolk, Virginia; 1987 - 1993

Associate Chief of Staff for Research and Development; Chief, Medical Research Service; VA Medical Center; Hampton, Virginia; 1987 - 1993

Adjunct Professor, Graduate College, Hampton University, Hampton, VA; 1992 - 1993

Associate Professor of Internal Medicine; Director, Clinical Nutrition Center; School of Medicine, University of California at Davis; Davis, California; 1983 - 1987

Assistant Professor of Internal Medicine; Director, Clinical Nutrition Center; University of Virginia School of Medicine, Charlottesville, Virginia, 1977 - 1983

Adjunct Lecturer in Health Studies; Pennsylvania State University, State College, Pennsylvania, 1978 - 1980

Adjunct Assistant Professor of Medicine; School of Medicine; University of California, Los Angeles, California, 1976 - 1977

Liaison Endocrinologist (Clinical Instructor), Vanderbilt University Medical Center, Nashville, Tennessee, 1973 - 1974

Chief, Department of Medicine; U.S. Army Hospital; Fort Campbell, Kentucky, 1973 - 1974

EDUCATION:

College:	B.A., Virginia Military Institute, Lexington, Virginia, 1960 -1964
Medical School:	M.D., Medical College of Virginia, Richmond, Virginia, 1964 -1968
Internship:	Medical College of Virginia, Richmond, Virginia (straight medicine), 1968-1969
Residency:	Harbor General Hospital, Torrance, California (Medicine), 1969-1970
Fellowship:	Walter Reed General Hospital, Washington, DC (Endocrinology-Metabolism), 1970-1972
	Harbor General Hospital, Torrance, California (Endocrinology-Metabolism), Research Fellowship, National Institute of Child Health and Human Development, 1974-1976
	Harbor General Hospital, Torrance, California, Chief Resident in Endocrinology, 1976-1977

BOARD CERTIFICATION:

Diplomate, American Board of Internal Medicine, June, 1972

Diplomate, Endocrinology and Metabolism, American Board of Internal Medicine, October, 1973

Diplomate, American Board of Nutrition, May, 1985

STATE CERTIFICATION:

Virginia: 1968 #19193
California: 1969 #C31542
Wisconsin: 1994 #35119

SOCIETY MEMBERSHIPS:

Fellow, American College of Physicians
Member, American Diabetes Association
Member, American Society of Bariatric Physicians
Member, American Society for Nutritional Sciences
Member, American Society for Clinical Nutrition
Member, American Society for Parenteral and Enteral Nutrition
Member, Endocrine Society
Member, North American Association for the Study of Obesity

ACTIVITIES AND HONORS:

Medical School:

Vice-President of the Student Body, School of Medicine, 1967 - 1968

Chairman of the Honor Council, 1967 - 1968

Vice-President, Alpha Sigma Xi Honorary Leadership Society, 1967 - 1968

Academic Committees:

Hospital Executive Committee, U.S. Army Hospital, Ft. Campbell, KY, 1973 - 1974

Department of Medicine Executive Committee, Harbor General Hospital, Torrance, CA, 1976 - 1977

Executive Committee, Diabetes Research & Training Center, University of Virginia Medical School, 1981 - 1983

Advisory Committee, Diabetes Research and Training Center, University of Virginia Medical School, **Chairman**, 1981 - 1983

Executive Committee, University of California, Davis, School of Medicine, 1985 - 1987

Vice Chairman of the Faculty, School of Medicine, University of California, Davis, 1985 - 1987

Medical Student Promotions Committee, University of California, Davis, **Chairman**, 1985 - 1987

Admissions Committee, Graduate Group in Nutrition, University of California, Davis, 1985 - 1987

Executive Committee, Clinical Nutrition Research Unit, University of California, Davis, 1985 - 1987

Director, Metabolic Core Laboratory, Clinical Nutrition Research Unit, University of California, Davis, 1985 - 1987

Research and Development Committee, VA Medical Center, Hampton, VA, **Secretary**, 1987 - 1993

Nutrition Committee, VA Medical Center, Hampton, VA, 1987 - 1989

Research Committee, Eastern Virginia Medical School, Norfolk, VA, 1987 - 1990

Committee on Committees, Eastern Virginia Medical School, Norfolk, VA, 1991 - 1993

Ethics Committee, VA Medical Center, Hampton, VA, 1993 - 1993

Dietary Committee, University of Wisconsin Hospital, 1994 -Present

Academic Committees (continued):

Space Committee, Dept. of Nutritional Sciences, University of Wisconsin, 1994- Present

Research Seminar Committee, Dept. of Nutritional Sciences, University of Wisconsin, 1994- Present

UW Foundation Committee, University of Wisconsin Hospital, 1994 - Present

Offices and Committees of Professional and Health Related Societies:

American Diabetes Association: **Vice President**, Virginia Affiliate, 1982 - 1983

American Institute of Biological Sciences, Scientific Peer Advisory and Review Services: Panel on US Army Research Institute of Environmental Medicine Field Ration Testing, 1998 - Present

American Institute of Nutrition (American Society for Nutritional Sciences)/American Society for Clinical Nutrition:
AIN/ASCN Membership Committee, 1986 - 1990; **Chairman**, 1989 - 1990
AIN/ASCN Public Information Committee, 1988 - 1990
ASCN Nominations Committee, 1990
Ad hoc Search Committee for the ASCN Executive Officer, **Chairman**, 1993
Ad hoc Committee on a Unifying Nutrition Certification Exam, **Chairman**, 1993
ASCN **Vice-President Elect**, 1992 - 1993
Vice-President, 1993 - 1994
President, 1994 - 1995
ASCN Nominations Committee, 1997

American Obesity Association: **Co-founder and President**, 1995 - Present

North American Association for the Study of Obesity:
1989 Annual Meeting Organizing Committee, **Chairman**
Vice President, 1988 - 1989
President-Elect, 1989 - 1990
President, 1990 - 1991
Education Committee, **Chair**, 1990 - 1992
Nominating Committee, 1992 (**Chair**); 1994

National Academy of Sciences, National Institutes of Health, Department of Health and Human Services, Department of Veterans Affairs, and World Health Organization Committees and Activities:

NIH Site Visit Committee, Program Project, Baylor University, Houston, TX, February, 1983.

NIH Site Review Committee, University of Alabama Medical School Multipurpose Arthritis Center Application, Birmingham, Alabama, January, 1984.

NIH Site Review Committee, Clinical Nutrition Research Center, Vanderbilt University, Nashville, Tennessee, April, 1984.

NIH Site Review Committee, Program Project, University of Pittsburgh, Pittsburgh, Pennsylvania, June, 1986.

National Academy of Sciences, National Institutes of Health, Department of Health and Human Services, Department of Veterans Affairs, and World Health Organization Committees and Activities (continued):

NIH Behavioral Neurobiology Study Section, Ad Hoc Reviewer, June, 1987.

Veterans Affairs Central Office, Merit Review Appeals Committee, 1987 - 1990

National Academy of Sciences, Food and Nutrition Board, Committee on Military Nutrition Research, 1989 - 1995

NIH Nutrition Study Section, Special Reviewer, November, 1989; February, 1991.

NIH, Planning Committee, Consensus Development Conference: Surgery for Severe Obesity, 1990 - 1991

NIH, Special Study Section for Obesity Research Centers, July, 1990

NIH, NIDDK: National Task Force on Prevention and Treatment of Obesity, 1991 - 1995

NIH, NIDDK Advisory Group on Clinical Nutrition Research Centers, 1991

NIH, Planning Committee, Technology Assessment Conference: Health Effects of Voluntary Weight Loss Efforts, 1991 - 1992

NIH Nutrition Study Section, Member, 1991 - 1995; **Chairman** 1993 - 1995

Veterans Affairs Central Office, Research Equipment Committee, 1992 - 1993

Health and Human Services, Office of Disease Prevention and Health Promotion, Nutrition Policy Staff Working Group on Healthy Weights, 1992 - 1994

Food and Drug Administration, Consultant, 1994 - 1995

National Academy of Sciences: Review Coordinator, *Report on Guidelines for Weight Control Programs*, 1994 - 1995

Health and Human Services, Office of Disease Prevention and Health Promotion: Senior Editorial Advisor, *Surgeon General's Report on Dietary Fat and Health*, 1994 - 1998

World Health Organization, Expert peer reviewer for *Obesity: Preventing and Managing the Global Epidemic - Report of a WHO Consultation on Obesity (WHO/NUT/98.1)*, 1997

NIH, Member, Advisory Committee: Working Group on Human Subjects (High Volume), 1998 - Present

National Institute on Aging, Member, Caloric Restriction Clinical Implications Advisory Group, 1998 - Present

MEETINGS ORGANIZED:

Chairman, Organizing Committee, Annual Meeting of the North American Association for the Study of Obesity, Bethesda, Maryland, September 13-16, 1989.

Chairman, Program Committee, American Institute of Nutrition Public Information Committee Symposium on Obesity, Annual Meeting: Federation of American Societies for Experimental Biology, Washington, D.C., April, 1990.

Chairman, Program Committee, Symposium on Very Low Calorie Diets, Satellite Symposium to the Sixth International Congress on Obesity, Kyoto, Japan, October 19-20, 1990.

Chairman, Program Committee, Symposium on Obesity, Congress of the Latin American Nutrition Society, San Juan, Puerto Rico, September 22-26, 1991.

Chairman, Organizing Committee, North American Association for the Study of Obesity Continuing Medical Education Conference, Atlanta, GA, November 30-December 1, 1991.

Chairman, Organizing Committee, Joint 9th Annual Virginia Nutrition Conference and North American Association for the Study of Obesity Continuing Medical Education Conference, Hampton, VA, March 5-7, 1992

Chairman, Organizing Committee, NIH Workshop: "Pharmacologic Treatment of Obesity", Atlanta, GA, September 1, 1992

Chairman, Organizing Committee, FASEB Symposium, "Controversies in Obesity," Experimental Biology Annual Meeting, New Orleans, LA, March 30, 1993

Chairman, Organizing Committee, American Society for Clinical Nutrition CME Course, " Nutrition and Cardiovascular Risk," Williamsburg, March 3-5, 1994

Co-Chairman, Organizing Committee, Satellite Symposium on Pharmacologic Treatment of Obesity, International Congress on Obesity, St. Adele, Quebec, Canada, August 18-20, 1994

Chairman, Planning Committee, First Annual Wisconsin Nutrition Continuing Education Conference, "Obesity Update '96," Madison, March 31-April 1, 1996.

MEDICAL JOURNAL ACTIVITIES:

Editorial Activities:

Contributing Editor - Nutrition Reviews, 1984 - 1992
Medical Advisory Board - Obesity Update, 1986 - 1993
Editorial Board - Journal of Nutrition, 1988 - 1992
Editorial Board - International Journal of Obesity, 1991 - present
Guest Editor, Volume 56 Supplement: "Very-Low-Calorie Diets", American Journal of Clinical Nutrition, 1992
Editorial Board, Section Editor, Obesity Research, 1992 - Present
Editorial Board, Weight Control Digest, 1997 - Present
Editorial Board, Diabetes Technology & Therapeutics, 1998 - Present

MEDICAL JOURNAL ACTIVITIES (continued):

Reviewer for: American Journal of Clinical Nutrition
American Journal of Physiology
American Journal of Public Health
Diabetes
Diabetes Care
Gastroenterology
International Journal of Obesity
Journal of the American Dietetic Association
Journal of Clinical Endocrinology and Metabolism
Journal of Clinical Investigation
Journal of Nutrition
New England Journal of Medicine
Physiology and Behavior
Science

HISTORY OF GRANT SUPPORT: (* Principal Investigator)

* "Effects of Exercise on Weight Loss and Metabolism in Obesity," Biomedical Research Support Subgrant, University of Virginia School of Medicine, 2/15/78 to 4/1/79, $5,000.

* "Metabolic Effects of Dieting and Weight Loss," Diabetes Research and Training Center Grant," NIH P30 AM17042, 6/1/77 to 8/31/79, $53,159.

* "Role of the Ileum in Regulating Food Intake in Rats," Diabetes Research and Training Center Grant," NIH P60 AM22125, 9/1/79 to 8/31/80, $10,500.

* "Humoral Mechanisms of Satiety," DHHS-NIADDKD 2 RO1 AM26225, 4/1/80 to 11/30/83, $101,940.

* "Humoral Mechanisms of Satiety," DHHS-NIADDKD 2 RO1 AM26225-S, (supplement) 1/1/81 to 11/30/83, $15,201.

* "Treatment of Obese Non-Insulin Dependent Diabetics with Home Glucose Monitoring and a Very Low Calorie Diet," Cambridge Quest Foundation, 5/1/82 to 4/30/84, $31,500.

* "Effects of Naltrexone on Body Weight, Metabolism, and Hormone Levels," DuPont Pharmaceuticals, 12/1/82 to 11/30/83, $152,499.

* "Zinc and Copper Metabolism in Obese Zucker Rats," Mead Johnson, Inc., 1/1/84 to 11/31/84, $6,480.

* "Endocrine, Metabolic, and Cardiovascular Effects of a Very Low Calorie Diet and Exercise," California Trim Plan, 3/1/84 to 2/28/85, $30,000.

* "Use of a Fiber Supplement for Weight Reduction," A. H. Robbins, 2/1/84 to 1/31/87, $250,000.

HISTORY OF GRANT SUPPORT: (* Principal Investigator)

* "Hormonal, Metabolic, and Behavioral Effects of Medium Chain Triglycerides in Obese Humans," Mead Johnson, Inc., 9/1/84-12/31/87, $80,000.

"Metabolic Core Laboratory, Core Director, Clinical Nutrition Research Unit," NIH 1 P30 AM35747 - 01, September 1, 1985 - August 31, 1990, $41,453

"Postprandial Changes in Plasma Lipids," Pilot Project, Clinical Nutrition Research Unit, NIH 1 P30 AM35747 - 01, September 1, 1985 - August 31, 1986, $9847, Co-investigator with P.A. Davis and B.O Schneeman.

* "Intestinal Mechanisms of Body Weight Regulation", VA Research Advisory Group Program, 2/1/88-9/30/88, $69,000.

* "Intestinal Mechanisms of Body Weight Regulation", VA Merit Review, 10/1/88-9/30/91, $207,195.

* "Molecular Mechanisms of Alterations in Energy Expenditure", Biomedical Research Support Grant, Eastern Virginia Medical School, Sponsor for Carol N. Boozer, Sc.D., Postdoctoral Fellow, 7/1/88-6/30/89, $2500.

* "Mechanisms of Weight Loss After Intestinal Surgery for Obesity", Biomedical Research Support Grant, Eastern Virginia Medical School, Sponsor for Patricia S. Choban, M.D., 7/1/88-6/30/89, $2500.

* "Glucose and Energy Metabolism with Acarbose Treatment", Miles Laboratories, 1/1/90-6/30/91, $31,000.

* "Evaluation of Anorectic Activity of Phenylpropanolamine Caplets in the Treatment of Obesity," Thompson Medical Company, 1/1/90-12/31/91, $104,000.

"Fuel Oxidation and Diet-Induced Obesity," Jeffress Foundation, 1/1/91-12/31/92. Principal Investigator - Carol N. Boozer, D.Sc., $41,400,

* "Lovan: Effect on Patient Adherence to a Diet Program and Evaluation of Responders and Non-responders to Determine Subtypes of Obesity," Eli Lilly Company, 12/1/91-11/30/94, $564,000.

* "Mechanisms of Weight Loss with Obesity Surgery," NIH RO1-DK43250, 9/1/91-8/31/95, $281,484.

* Beers-Murphy Clinical Nutrition Center, University of Wisconsin, Madison, 12/1/93-Present, $1,855,000.

* Regulation of Energy Balance: Intestinal Mechanisms; NIH RO1 DK44397, 7/1/97-6/30/00, $436,974.

* "Animal Models of Virus Induced Obesity," NIH RO1 DK52227, 9/30/97-9/29/00, $444,582

* "The Effects of Conjugated Linoleic Acid in Obese Humans," Natural Nutrition, Inc., 9/15/97-9/14/99, $175,000.

HISTORY OF GRANT SUPPORT: (* Principal Investigator)

* A Comparison of the Long Term Efficacy of Self-Help Weight Loss Versus a Commercial Weight Loss Program. Weight Watchers Foundation, 4/15/98-10/14/00, $114,363.

* Comparison of the prevalence of cardiac valvular abnormalities in patients treated with the combination fenfluramine and phentermine for at least three consecutive months versus untreated controls, as assessed by echocardiogram. Wyeth-Ayerst Laboratories, 4/20/98-4/19/99, Approximately $60,000.

* Treatment of Obesity with Phentermine and Fluoxetine, Eli Lilly, 4/30/98-4/29/99, $19,396

* Comparison of echocardiograms and clinical outcomes of patients previously treated with phentermine-fenfluramine vs phentermine-fluoxetine. Eli Lilly, 6/30/98-6/29/99, $93,563.

Non-invasive measurement of energy expenditure in man, NIH R01-DK30031, 4/1/95-3/31/00, $470,953 (PI: DA Schoeller)

PENDING GRANT SUPPORT: (* Principal Investigator)

* Use of Conjugated Linoleic Acid in Diary Products to Prevent Weight Regain or Alter Body Composition Following a Very Low Calorie Diet in Obese People; Dannone, Inc., 4/1/99-10/31/00, $215,000

Non-human Primate Model for Human Adenovirus Induced Obesity, NIH, 12/1/99-11/30/02, $199,998 (PI: NV Dhurandhar)

Obesity and Fibromyalgia: Symptom Expression and Physiology, NIH, 3/1/99-2/28/2003, $311,793 (PI: D Muller)

* Adenovirus & Human Obesity-Longitudinal and Twin Studies, NIH, 7/1/99-6/30/04, $1,100,000.

* University of Wisconsin Clinical Nutrition Research Unit (CNRU), NIH, 7/1/99-6/30/04, $3,750,000

MILITARY SERVICE:

Endocrine Fellow, Walter Reed Army Hospital, Washington, D.C., 1970 - 1972

Division Surgeon, 101st Airborne Division, Fort Campbell, KY, 1973 - 1974

Chief, Dept. of Medicine, U.S. Army Hospital, Fort Campbell, KY, 1973-1974

Army Commendation Medal, Fort Campbell, KY, 1974

INVITED LECTURES: (over 250 invited national and international lectures)

1997 lectures (outside Madison, WI):

American Diabetes Association Annual CME Course
Rivendell Psychiatric Hosp, Bowling Green, KY
University of Medicine and Dentistry of New Jersey, New Brunswick, NJ
University of North Carolina, Chapel Hill, NC
American Society of Bariatric Physicians CME Course, New Orleans, LA
American Association of Clinical Endocrinologists CME Course, Philadelphia, PA
American College of Physicians CME Lecture, Washington, DC
Health Learning Systems, Tucson, AZ
Northeastern Ohio Universities, Akron, OH
Endocrine Club, Washington, DC
XI Annual Congress on Metabolism and Nutrition Support, Medellin, Columbia
Grant Hospital CME lecture, Columbus, OH
Endocrine Society Annual Meeting, Minneapolis, MN
Hennepin County Hospital, Minneapolis, MN
16th International Congress of Nutrition, Montreal, Canada
American Association of Clinical Endocrinologists, Montreal, Canada
Fox Valley Medical Society, Door County, WI
Federal Trade Commission, Washington, DC
American Society of Bariatric Physicians Annual Meeting, New Orleans, LA
Interstate Postgraduate Medical Society Annual Meeting, Las Vegas, NV
Institute of Nutrition, University of North Carolina, Chapel Hill, CME Conference
North American Association for the Study of Obesity Annual CME Course, Cancun, Mexico

1998 lectures (outside Madison, WI):

Novartis Corporation, Basel, Switzerland
American Society for Parenteral and Enteral Nutrition Annual Meeting, Orlando, FL
Janssen-Cilag/Ortho McNeil, International Top Opinion Leader Seminar, London, England
American Diabetes Association Annual CME Course, San Francisco, CA
Academy of Medicine, Milwaukee, WI
Trout Lecture, Michigan State University, Lansing, MI
University of Kentucky, Lexington, KY
Law Journal Seminar, New York, NY
Gunderson Clinic, LaCrosse, WI
Endocrine Society Annual Meeting, New Orleans, LA
Obesity Research Network CME Course, New Orleans, LA
NIH International Symposium on Obesity, Charleston, SC
University of Minnesota Medical Grand Rounds, Minneapolis, MN
St. Louis University Medical School, CME Course, St. Louis, MO
Wisconsin Academy of Family Physicians, CME Course, Waukesha, WI
Zeneca Corporation, Brugge, Belgium
Cornell University Medical School, Memorial Sloan-Kettering Hospital, New York, NY

BIBLIOGRAPHY

A. MANUSCRIPTS:

1973 1. Dimond RC, Brammer SR, Atkinson RL, Howard WJ, Earll JM, Chlorpromazine treatment and growth hormone secretory responses in acromegaly. Journal of Clinical Endocrinology and Metabolism 36:1189-1195, 1973.

1973 2. Atkinson RL Medroxyprogesterone for acromegaly. Journal of the American Medical Association 223:442, 1973 (Letter).

1973 3. Toppell KL, Atkinson RL, Whitcomb ME. Lung growth in acromegaly. American Review of Respiratory Disease 108:1254-1258, 1973.

1974 4. Atkinson RL, RC Dimond, WJ Howard, JM Earll. Unsuccessful treatment of acromegaly with medroxyprogesterone acetate. Acta Endocrinologica 77:19-25, 1974.

1974 5. Atkinson RL, JM Earll. Munchausen syndrome with renal stones. Journal of the American Medical Association 230:89, 1974.

1974 6. Becker DP, RL Atkinson, R Sakalas, JK Vries, HF Young, FS Vines, J Martinez. Transphenoidal microsurgery for acromegaly: successful treatment with preservation of pituitary function. Confina Neurologica 36:101-105, 1974.

1975 7. Atkinson RL, DP Becker, AN Martins, M Schaaf, RC Dimond, L Wartofsky, JM Earll. Acromegaly: treatment by transsphenoidal microsurgery. Journal of the American Medical Association 233:1279-1283, 1975.

1976 8. Bray GA, WT Dahms, FL Greenway, M Marriott, M Molitch, RL Atkinson. Evaluation of the obese patient. II. Clinical findings. Journal of the American Medical Association 235:2008-2010, 1976.

1977 9. Bray, GA, RL Atkinson. Factors affecting basal metabolic rate. Progress in Food and Nutrition Science 2:395-403, 1977.

1977 10. Rodin J, GA Bray, RL Atkinson, WT Dahms, FL Greenway, K Hamilton, M Molitch. Predictors of successful weight loss in an outpatient obesity clinic. International Journal of Obesity 1:79-87, 1977.

1977 11. Atkinson RL, FL Greenway, GA Bray, WT Dahms, ME Molitch, K Hamilton, J Rodin. Treatment of obesity: comparison of physician and nonphysician therapists using placebo and anorectic drugs in a double-blind trial. International Journal of Obesity 1:113-120, 1977.

1977 12. Bray GA, FL Greenway, RE Barry, JR Benfield, RL Fiser, WT Dahms, RL Atkinson, and AA Schwartz. Surgical treatment of obesity: a review of our experience and an analysis of published reports. International Journal of Obesity 1:331-367, 1977.

1977 13. Glass AR, RS Swerdloff, GA Bray, WT Dahms, RL Atkinson. Low serum testosterone and sex-hormone-binding- globulin in massively obese men. Journal of Clinical Endocrinology and Metabolism 45:1211-1219, 1977.

1978 14. Atkinson RL, WT Dahms, GA Bray, R Jacob, HH Sandstead. Plasma zinc and copper in obesity and after intestinal bypass. Annals of Internal Medicine 89:491-493, 1978.

1978 15. Atkinson RL, WT Dahms, GA Bray, AA Schwartz. Parathyroid hormone levels in obesity: effects of intestinal bypass surgery. Mineral and Electrolyte Metabolism 1:315-320, 1978.

1978 16. Atkinson RL, WT Dahms, DA Fisher, AL Nichols. Occult thyroid disease in an elderly hospitalized population. Journal of Gerontology 33:372-376, 1978.

1978 17. Bray GA, B Zachary, WT Dahms, RL Atkinson, TH Oddie. Direct vs. indirect measurements: eating patterns of massively obese individuals. Journal of the American Dietetic Association 72:24-27, 1978.

1978 18. Glass AR, WT Dahms, G Abraham, RL Atkinson, GA Bray, RS Swerdloff. Secondary amenorrhea in obesity: etiologic role of weight-related androgen excess. Fertility and Sterility 30:243-244, 1978.

1978 19. Bray GA, FL Greenway, ME Molitch, WT Dahms, RL Atkinson, K Hamilton. Use of anthropometric measures to assess weight loss. American Journal of Clinical Nutrition 31:769-773, 1978.

1978 20. Dahms WT, ME Molitch, GA Bray, FL Greenway, RL Atkinson, K Hamilton. Treatment of obesity: cost-benefit assessment of behavioral therapy, placebo, and two anorectic drugs. American Journal of Clinical Nutrition 31:774-778, 1978.

1978 21. Atkinson RL, GA Bray. Energy balance in obesity and its relationship to diabetes mellitus. Advances in Modern Nutrition 2:373-393, 1978.

1978 22. Chiasson JL, RL Atkinson, AD Cherrington, U Keller, BC Sinclair-Smith, WW Lacy, JE Liljenquist. Effects of fasting on gluconeogenesis from alanine in nondiabetic man. Diabetes 28:56-60, 1978.

1979 23. Bray GA, WT Dahms, RL Atkinson, J Rodin, I Taylor, C Frame, A Schwartz. Metabolic and behavioral differences between dieting and intestinal bypass. Hormone and Metabolic Research 11:648-654, 1979.

1979 24. Bray GA, WT Dahms, RL Atkinson, I Mena, I Taylor, J Rodin, A Schwartz, C Frame. The control of food intake: effects of dieting and intestinal bypass. Surgical Clinics of North America 59:1043-1054, 1979.

1979 25. Atkinson RL, WT Dahms, GA Bray, C Lemmi, AA Schwartz. Gastrin secretion after weight loss by dieting and intestinal bypass surgery. Gastroenterology 77:696-699, 1979.

1979 26. Atkinson RL Nutrition vs. obesity. In The Medicine Called Nutrition, H.A. Guthrie and D.T. Mason (editors). Medcom, Inc., New York, N.Y., pp 40-47, 1979.

1979 27. Atkinson RL Parathyroid hormone and age. New England Journal of Medicine 301:841, 1979 (Letter).

1980 28. Atkinson RL Management of the obese, insulin-independent diabetic. Practical Cardiology 6:54-68, 1980.

1980 29. Bray GA, WT Dahms, RL Atkinson, I Mena, A Schwartz. Factors controlling food intake: a comparison of dieting and intestinal bypass. American Journal of Clinical Nutrition 33:376-382, 1980.

1980 30. Chiasson JL, RL Atkinson, AD Cherrington, U Keller, BC Sinclair-Smith, WW Lacy, JE Liljenquist. Effects of insulin at two dose levels on gluconeogenesis from alanine in fasting man. Metabolism 29:810-818, 1980.

1980 31. Stevens J, RL Atkinson, SL Pohl. Insulin-induced insulin resistance of lipolysis in human adipocytes in organ culture. Journal of Clinical Endocrinology and Metabolism 51:921-924, 1980.

1980 32. Atkinson RL. Pharmacologic treatment of obesity. Hospital Formulary 15:882-888, 1980.

1980 33. Bray GA, WT Dahms, RL Atkinson, J Rodin, I Taylor, A Schwartz, C Frame, I Mena. Effects of dieting and intestinal bypass on food intake. In Surgical Management of Obesity, J.D. Maxwell, J. C. Gazet, and T.R.E. Pilkington (editors). Academic Press, London, pp 77-91, 1980.

1981 34. Dahms WT, P Nilsson-Ehle, AS Garfinkel, RL Atkinson, GA Bray, M Schotz. Lipoprotein lipase activity in adipose tissue from obese human beings. International Journal of Obesity 5:81-84, 1981.

1981 35. Atkinson RL, WT Dahms, GA Bray, MA Sperling. Adrenergic modulation of glucagon and insulin secretion in obese and lean humans. Hormone and Metabolic Research 13:249-253, 1981.

1981 36. Atkinson RL, DL Kaiser. Nonphysician supervision of a very-low calorie diet. Results in over 200 cases. International Journal of Obesity 5:237-241, 1981.

1981 37. Pohl SL, J Stevens, RL Atkinson. Acute and chronic regulation of lipolysis and glucose metabolism in human adipose tissue. In Recent Advances in Obesity Research. Proceedings of the Third International Congress on Obesity, John Libbey & Co., Ltd., London, pp 367-373, 1981.

1982 38. Atkinson, RL Intravenous lidocaine for the treatment of intractable pain of adiposis dolorosa. International Journal of Obesity 6:351-357, 1982.

1982 39. Atkinson RL, JH Whipple, SH Atkinson, and CS Stewart. Role of the small bowel in regulating food intake in rats. American Journal of Physiology 242:R429-R433, 1982.

1982 40. Atkinson RL and EL Brent. Appetite suppressant activity in plasma of rats after intestinal bypass surgery. American Journal of Physiology 243:R60-R64, 1982.

1982 41. Atkinson RL, EL Brent, JH Whipple. Altered dietary preference for fat and sucrose after intestinal bypass surgery in rats. International Journal of Obesity 6:499-506, 1982.

1982 42. Atkinson RL. Naloxone decreases food intake in obese humans. Journal of Clinical Endocrinology and Metabolism 55:196-198, 1982.

1982 43. Bibbs ML, RL Atkinson. Obesity and diabetes: their relationship and treatment. Occupational Health Nursing 30:33-36, 1982.

1983 44. Suratt PM, SC Wilhoit, RL Atkinson. Elevated pulse flow resistance in awake obese subjects with obstructive sleep apnea. American Review of Respiratory Disorders 127:162-165, 1983.

1983 45. Suratt PM, P Dee, RL Atkinson, P Armstrong, SC Wilhoit. Fluoroscopic and computed tomographic features of the pharyngeal airway in obstructive sleep apnea. American Review of Respiratory Disorders 127:487-492, 1983.

1983 46. Bray GA, WT Dahms, FL Greenway, MM Solares, M Molitch, RL Atkinson. Clinical findings in obesity. In Using the Clinical Laboratory in Medical Decision-Making, G.D. Lundberg (editor). American Society of Clinical Pathologists Press, Chicago, pp 117-121, 1983.

1983 47. Atkinson RL, EL Brent, BS Wagner, JH Whipple. Energy balance and regulation of body weight after intestinal bypass surgery in rats. American Journal of Physiology 245:R658-R663, 1983.

1983 48. Atkinson RL Book review of "Health and Obesity," P.T. Kuo, H.H. Conn and E.A. DeFelice (editors). Journal of the American Medical Association 250:1471-1472, 1983.

1983 49. Bray GA, WT Dahms, RS Swerdloff, RH Fiser, RL Atkinson, RE Carrel. The Prader-Willi syndrome: a study of 40 patients and a review of the literature. Medicine 62:59-80, 1983.

1984 50. Atkinson RL Effects of fad diets for weight reduction. In P.C. White, (Ed). Malnutrition: Determinants and Consequences, Alan R. Liss Publishers, Inc., New York, pp 405-413, 1984.

1984 51. Atkinson RL, CS Russ, PA Ciavarella, ES Owsley, ML Bibbs. A comprehensive approach to outpatient obesity management. Journal of the American Dietetic Association 84(4):439-444, 1984.

1984 52. Russ CS, PA Ciavarella, RL Atkinson. A comprehensive outpatient weight reduction program: Dietary patterns, psychological considerations, and treatment principles. Journal of the American Dietetic Association 84(4):444-446, 1984.

1984 53. Suratt PM, SC Wilhoit, HS Hsiao, RL Atkinson, DF Rochester. Compliance of chest wall in obese subjects. Journal of Applied Physiology 57:403-407, 1984.

1984 54. Burke L, JA Owen, RL Atkinson. Allergies to human insulin. Diabetes Care 7(4): 402-403, 1984.

1984 55. Atkinson RL Endocrine and metabolic effects of opiate antagonists. Journal of Clinical Psychiatry 45:9(2),20-24, 1984.

1985 56. Anonymous review. Alterations in metabolic rate after weight loss in obese humans. Nutrition Reviews 43:41-42, 1985.

1985 57. Anonymous review. Dietary carbohydrate intake and catecholamine secretion in man. Nutrition Reviews 43:138-140, 1985.

1985 58. Atkinson RL, DL Kaiser. Effects of calorie restriction and weight loss on glucose and insulin levels in obese humans. Journal of the American College of Nutrition 4:411-419, 1985.

1985 59. Russ CS, RL Atkinson. Use of high fiber diets for the outpatient treatment of obesity. Nutrition Reports International 32:193-198, 1985.

1985 60. Anonymous review. Diarrhea and malabsorption associated with the acquired immunodeficiency syndrome (AIDS). Nutrition Reviews 43:235-237, 1985.

1985 61. Atkinson RL. Etiology, pathophysiology and treatment of obesity. In: Dietary Excesses and Health/Disease Implications, J.B. Anderson (ed). University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, 1985.

1985 62. Altschul AM, RL Atkinson, GL Blackburn, J Grommet, RL Weinsier. Proposed guidelines for professional weight control programs. In: Recent Advances in Obesity Research: IV. Proceedings of the 4th International Congress on Obesity (1983), Hirsch, J. and T.B. Van Itallie (eds), John Libbey Publishers, London, pp 267-270, 1985.

1985 63. Atkinson RL, PM Suratt, SC Wilhoit, L Recant. Naloxone improves sleep apnea in obese humans. International Journal of Obesity 9:233-239, 1985.

1985 64. Atkinson RL, LK Berke, CR Drake, ML Bibbs, FL Williams, DL Kaiser. Effects of long term therapy with naltrexone on body weight in obesity. Clinical Pharmacology and Therapeutics 38:419-422, 1985.

1985 65. Russ CS, RL Atkinson. Comments on the Army weight control program: a critical view. Journal of the American Dietetic Association 85:1435-1436, 1985.

1985 66. Atkinson RL Book review of "Nutritional Intervention in the Aging Process." H.J. Armbrecht, J.M. Prendergast and R.M. Coe (eds). Springer-Verlag, NY, 1984. Journal of Gerontology 40:650, 1985.

1985 67. Atkinson RL, LK Berke, DL Kaiser, SL Pohl. Effects of very low calorie diets on glucose tolerance and diabetes mellitus in obese humans. In: Management of Obesity by Severe Caloric Restriction. GL Blackburn and GA Bray (editors). PSG Publishing Co, Inc, pp 279-280, 1985.

1986 68. Atkinson RL Very low calorie diets: getting sick or remaining healthy on a handful of calories. Journal of Nutrition 116 (5): 918-920, 1986.

1986 69. Pfohl DN, JI Allen, RL Atkinson, DS Knopman, RJ Malcolm, JE Mitchell, JE Morley. Naltrexone hydrochloride (Trexan): A review of serum transaminase elevations at high dosage. In: Problems of Drug Dependence, 1985, Proceedings of the 47th Annual Scientific Meeting, The Committee on Problems of Drug Dependence, Inc. L.S. Harris (ed.). NIDA Research Monograph 67, Rockville, MD, pp 66-72, 1986.

1986 70. Anonymous review. The genetics of obesity. Nutrition Reviews 44:199-200, 1986.

1987 71. Levine AS, RL Atkinson. Opioids in the regulation of food intake and energy expenditure. Federation Proceedings 46:159-162, 1987.

1987 72. Atkinson RL. Opioid regulation of food intake and body weight in humans. Federation Proceedings 46:178-182, 1987.

1987 73. Anonymous review. Absorption of soy protein and minerals in ileostomy patients. Nutrition Reviews 45(6):166-167, 1987.

1988 74. Atkinson RL, CR Waggoner, DL Kaiser. Food intake and nutrient selection in obese humans on long term naltrexone therapy. Nutrition Reports International 37:555-563, 1988.

1988 75. Atkinson RL. Medical Management of VLCD in NIDDM. Diabetes Care and Education 9: No. 6, Nov. 1988.

1989 76. Anonymous review. Energy expenditure and the control of body weight. Nutrition Reviews 47:249-252, 1989

1989 77. Atkinson RL Low and Very Low Calorie Diets. Medical Clinics of North America, 73:203-215, 1989.

1989 78. Atkinson RL. Future Directions of Nutrition Research: Science, Public Health, Public Policy. Journal of Nutrition 119:669-670, 1989.

1989 79. Moyer CL, RG Holly, EA Amsterdam, RL Atkinson. The effects of cardiac stress during a very low calorie diet and exercise program in obese women. American Journal of Clinical Nutrition 50:1324-1327, 1989.

1989 80. Brenner CJ, RL Atkinson. Short bowel syndrome: a case report. Nutrition Reviews 47:350-353, 1989.

1990 81. Chen DC, JS Stern, RL Atkinson. Effects of ileal transposition on food intake, dietary preference, and weight gain in Zucker rats. American Journal of Physiology 258:R269-R273, 1990.

1990 82. Boozer CN, Choban PS, RL Atkinson. Ileal transposition surgery attenuates the increased efficiency of weight gain on a high fat diet. International Journal of Obesity 14:869-878, 1990.

1991 83. Atkinson RL. Massive obesity: complications and treatment. Nutrition Reviews 49:49-53, 1991.

1991 84. Lauterio TJ, RL Atkinson. Nutritional aspects of pharmacology. In: Human Pharmacology: Molecular to Clinical, Editors: LB Wingard, TM Brody, J Larner, A Schwartz. 1991, pp 820-830.

1991 85. Atkinson, R.L. Usefulness and limits of VLCD in the treatment of obesity. In: Progress in Obesity Research: 1990. Editors: Y Oomura, S Tarui, S Inoue, T Shimazu, John Libbey, London, 1991, pp 473-480.

1992 86. Atkinson RL. Low calorie diets and obesity. In: Biotechnology and Nutrition, Editors: DB

Bills, SD Kung, Butterworth-Heinemann, Boston, 1992, pp 29-45.

1992 87. Bray GA, Atkinson RL. New weight guidelines for Americans. American Journal of Clinical Nutrition 55:481-482, 1992 (letter).

1992 88. Atkinson RL. Medical evaluation and monitoring of patients treated by severe caloric restriction. In: Treatment of the Seriously Obese Patient, Editors: Wadden TA, Van Itallie TB, Guilford Press, New York, 1992, pp 273-289.

1992 89. Atkinson RL, Fuchs A, Pastors JG, Saunders JT. Combination of very-low-calorie diet and behavior modification in the treatment of obesity. American Journal of Clinical Nutrition, 56(1 Suppl): 199S-202S, 1992.

1992 90. Atkinson, RL. Obesity. In: Conn's Current Therapy, Editor: Rakel RE, WB Saunders Publishers, Philadelphia, 1992, pp 551-557.

1992 91. West DB, Boozer CN, Moody DL, Atkinson RL. Dietary obesity in nine inbred mouse strains. American Journal of Physiology, 262:R1025-R1032, 1992.

1992 92. Atkinson RL. Editorial: Treatment of obesity. Nutrition Reviews, 50:338-339, 1992.

1993 93. Atkinson RL. Proposed standards for judging success of the treatment of obesity. Annals of Internal Medicine, 119:677-680, 1993.

1993 94. St. Jeor ST, Brownell KD, Atkinson RL, Bouchard C, Dwyer J, Foreyt JP, Heber D, Kris-Etherton P, Stern JS, Willett W, Wilson GT, Wood PD. Obesity: Workshop III. AHA Prevention Conference III Behavior Change and Compliance: Keys to Improving cardiovascular health. Circulation 88:1391-1396, 1993.

1993. 95. Boozer CN, Brasseur A, Atkinson RL. Dietary fat affects weight loss and adiposity during energy restriction in rats. American Journal of Clinical Nutrition 58:846-852, 1993.

1994 96. Greenway FL, Raum WJ, Atkinson RL. Higher calorie content preserves myocardial electrical activity during very low calorie dieting. Obesity Research 2:95-99, 1994.

1994 97. Atkinson RL, Walberg-Rankin J. Physical activity, fitness and severe obesity. In: Physical Activity, Fitness and Health, Editors: Bouchard C, Shephard RJ, Stephens T, Human Kinetics Publishers, Champaign, 1994, pp 696-711.

1994 98. Atkinson RL. The role of drugs in weight control. Weight Control Digest 4(2):339-340, 1994.

1994 99. Atkinson RL, Hubbard VS. Report on the NIH workshop on pharmacologic treatment of obesity. American Journal of Clinical Nutrition 60:153-156, 1994.

1994 100. Eberhart GP, West DB, Boozer CN, Platt KH, Atkinson RL. Effect of high fat feeding on insulin sensitivity of adipocytes from mouse strains resistant or sensitive to diet induced obesity. American Journal of Physiology 266:R1423-R1428, 1994.

1994 101. Atkinson RL. Obesity. Encyclopaedia Britannica Medical and Health Annual, Editor: Bernstein E, Encyclopaedia Britannica Inc., Chicago, 1994, pp 337-342.

1994 102. Sayler ME, Goldstein DJ, Roback PJ, Atkinson RL. Evaluating success of weight loss programs, with an application to fluoxetine weight reduction clinical trial data. International Journal of Obesity 18:742-751, 1994.

1994 103. Atkinson RL, Dietz WH, Foreyt JP, Hill JO, Pi-Sunyer FX, Wing R, Goodwin NJ, Weinsier RL, Hirsch J. Towards prevention of obesity: research directions. Obesity Research 2:571-584, 1994.

1994 104. Atkinson RL. Genetic factors influence the response of energy metabolism, body weight, and body composition to exercise. Obesity Research 2:470-471, 1994.

1995 105. Boozer CN, Atkinson RL. Dietary fat and adiposity: a dose-response relationship in adult rats fed isocalorically. American Journal of Physiology 268:E546-550, 1995.

1995 106. Atkinson RL. Managing chronic refractory obesity. In: Eating Disorders and Obesity. Editors: Brownell KD, Fairburn CG, Guilford Press, New York, 1995, pp 524-530.

1995 107. Hotamisligil GS, Amer P, Caro JF, Atkinson RL, Spiegelman BM. Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity and insulin resistance. Journal of Clinical Investigation 95:2409-2415, 1995.

1995 108. Atkinson RL, Blank RC, Loper JF, Schumacher D, Lutes R. Combined drug treatment of obesity. Obesity Research 3(Suppl 4):497S-500S, 1995.

1996 109. Choban PS, Atkinson RL, Moore BJ, et al. Guidance for Treatment of Adult Obesity. Shape Up America!, Bethesda, 1996.

1996 110. Atkinson RL. Role of nutrition planning in the treatment for obesity. Endocrinology and Metabolism Clinics of North America 25:955-964, 1996.

1996 111. Caterson ID, Atkinson RL, Bray GA, Hansen BC, Reeds PJ, Stock MJ, Tremblay A, York DA. Group Report: What are the animal and human models for the study of regulation of body weight and what are their respective strengths and limitations? In: Regulation of Body Weight: Biological and Behavioral Mechanisms, Editors: Bouchard C, Bray GA. 1996 pp 85-110.

1996 112. Atkinson, RL. Mechanisms of weight loss with obesity surgery. In: A. Angel, H. Anderson, C. Bouchard, D. Lau, L. Leiter and R. Mendelson (eds.). Progress in Obesity Research: 7. Proceedings of the 7th International Congress on Obesity. London, England, John Libbey & Company Ltd, 1996, pp. 613-620.

1997 113. Krugner-Higby L, Wolden-Hanson T, Gendron A, Atkinson, RL. High Prevalence of Gastric Trichobezoars (Hair Balls) in Wistar-Kyoto Rats Fed a Semi-Purified Diet. Lab Animal Sci, 46:635-639.

1997 114. Dhurandhar NV, Atkinson RL. Appetite-suppressant drugs and primary pulmonary hypertension. N Engl J Med 336:511, 1997.

1997 115. Hotamislilgil GS, Amer P, Atkinson RL, Spiegelman BM. Differential regulation of the p80 tumor necrosis factor receptor in human obesity and insulin resistance. Diabetes 46:451-455, 1997.

1997 116. Atkinson RL, Dhurandhar NV. Recent advances in the drug treatment of obesity. Weight Control Digest 7: 601-607, 1997.

1997 117. Atkinson RL. Use of drugs in the treatment of obesity. Annual Review of Nutrition 17:383-403, 1997.

1997 118. Dhurandhar NV, Atkinson RL. Drug treatment of obesity: guidelines for an outpatient treatment program. American Journal of Bariatric Medicine. Summer, 1997:18-23.

1997 119. Atkinson RL. Obesity surgery as a model for understanding the regulation of food intake and body weight. American Journal of Clinical Nutrition. 66:184-185, 1997.

1997 120. Atkinson RL, Stern JS. Weight cycling: definitions, mechanisms, and problems with interpretation. In: Handbook of Obesity, Editors: Bray GA, Bouchard C. Marcel Dekker, Inc., New York, 1997, pp 791-804.

1997 121. Spitz AF, Schumacher D, Blank RC, Dhurandhar NV and Atkinson RL. Long-term pharmacologic treatment of morbid obesity in a community practice. Endocrine Practice 3:269-275, 1997.

1997 122. Atkinson RL. Recent advances in the pharmacological control of energy balance and body weight. In: Lipids and Syndromes of Insulin Resistance. Annals of the New York Academy of Sciences. Editors: Klimes I, Haffner SM, Sebokova E, Howard BV, Storlian LH. 827:449-460, 1997

1997 123. Atkinson RL. Nutritional aspects of pharmacology. In: Human Pharmacology: Molecular to Clinical, Editors: LB Wingard, TM Brody, J Larner, A Schwartz. Mosby Year-Book, St. Louis, 1997, pp 843-860.

1997 124. Dhurandhar NV, Kulkarni PR, Ajinkya SM, Sherikar AA, Atkinson RL. Association of adenovirus infection with human obesity. Obesity Research 5:464-469, 1997.

1997 125. Atkinson RL, Blank RC, Schumacher D, Dhurandhar NV, Ritch DL. Long term drug treatment of obesity in a private practice setting. Obesity Research 5:578-586, 1997.

1998 126. Dhurandhar NV, Atkinson RL. Complications of obesity. Encyclopedia of Human Nutrition. Ed: Sadler M, Caballero B, Strain S. Academic Press, 1998

1998 127. Atkinson RL. What have we learned from the phen-fen debacle? The Weight Control Digest, Volume 8, Number 2, March/April 1998, p. 698.

1998 128. Lonergan RP 3rd, Ware JC, Atkinson RL, Winter WC, Suratt PM. Sleep apena in obese miniature pigs. Journal of Applied Physiology, 84:531-536, 1998.

1998 129. Atkinson, RL. Guidelines for the initiation of obesity treatment. Journal of Nutritional Biochemistry, 9:546-552, 1998.

1998 130. Atkinson RL, Dhurandhar NV. Recent advances in obesity research. Encyclopaedia Britannica Medical and Health Annual, Editor: Bernstein E, Encyclopaedia Britannica Inc., Chicago.

1998 131. Wolden-Hanson T, Gidal B, Atkinson RL. Evaluation of a rat model of valproate-induced

obesity. Pharmacotherapy 18:1075-1081, 1998.

Manuscripts in Press:

132. Atkinson RL. Etiologies of obesity. In: Obesity: Practical Aspects. Editor: D. Goldstein. In press.

133. Atkinson, RL. Practical aspects of obesity treatment: combination therapies. In: Obesity: Practical Aspects. Editor: D. Goldstein. In press.

134. Dhurandhar NV, Atkinson RL. Pharmacological management of the obese patient. Textbook of Medicine, Exercise, Nutrtition and Health. In press.

135. Atkinson, RL. Conjugated linoleic acid for altering body composition and treating obesity. Ed: Yurawecz MP, Mossoba MM, Kramer JKG, Nelson G, Pariza MW. American Oil Chemists' Society Press. In press.

136. Atkinson RL. Drug therapy for obesity. N Engl J Med. In review.

B. ABSTRACTS: Over 130 abstracts published or in press.

APPENDIX C

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Julio L. Pimentel
Title:	Decreased Fat Absorption with an Anti-Lipase Antibody
Serial No.:	08/888,202
Filed:	July 7, 1997
Examiner:	Ungar
Group Art Unit:	1642

SUPPLEMENTAL DECLARATION UNDER 37 CFR §1.132

Commissioner of Patents & Trademarks
Washington, D.C. 20231

I, Richard Lee Atkinson, Jr., M.D., do hereby declare as follows:

(1) I have read the Office Action identified as Paper No. 13 and have reviewed the references relied upon by the Examiner in support of the rejection of claims.

(2) In my prior Declaration of August 6, 1999, I considered each of those references (except for the newly-cited Sterling reference) and stated why I considered them to be in non-analogous fields so that one skilled in the art would not be expected to combine them in the manner proposed by the Examiner. While I remain of that view, I will nevertheless respond to the latest Action, and to prior Actions, as if all of the references were properly combinable as asserted by the Examiner.

(3) As stated on pages 4 and 5 of my earlier Declaration, before I read the specification and claims of the present application (08/888,202), I would have been skeptical that lipase antibodies introduced orally into the gastrointestinal tract of post-newborn non-ruminant mammals would have any significant effect in inhibiting pancreatic lipase activity. The teachings of all of the references of record, taken in combination, would not have led me to a different conclusion, and I do not believe others skilled in the art would have considered the claimed invention to be obvious from the combined teachings of such references for the reasons set forth below.

(4) As previously stated, gastric acid and protein digestive enzymes in a post-newborn or post-suckling non-ruminant mammal would be expected to destroy antibodies before they reach the point in the digestive tract where pancreatic lipase enters. I do not find that the references of record disclose or suggest otherwise.

(5) The Hadvary patent (4,598,089) is relied upon by the Examiner as a main reference with which up to a total of nine other references are combined. The Hadvary patent concerns the use of tetrahydrolipstatin, now widely known under its trade name Xenical, which is a molecule clearly different and completely unrelated to avian-derived pancreatic lipase antibodies. If anything, Hadvary directs the reader away from the oral administration of antibodies for reducing fat absorption in a recipient, much less a healthy, post-suckling, non-ruminant mammallian recipient.

(6) The secondary references do disclose that antibodies may be administered to mammals for

various purposes, but those references fail to make up for Hadvary's shortcomings for one or more of a number of reasons. The Moloney, Flint, Ohkaru and Japanese (02150294) references are concerned with procedures in which antibodies are administered intravenously, subcutaneously, or intraperitoneally, but I do not find of them disclosing or suggesting that antibodies might be effectively administered orally. While the effect of antibodies inhibiting lipase activity is well known, I believe it is surprising and unexpected that such activity would be retained if the antibodies were orally administered to a healthy adult non-ruminant mammal, and I find nothing in these references to the contrary.

(7) It is also well known that antibodies in a mother's milk are capable of traveling through the digestive tract of nursing offspring and of retaining their activity in the not yet fully developed digestive systems of such offspring. The Tokoro and Martin et al references disclose oral administration of antibodies to mammals in the suckling period of post natal development. While it is not surprising that such antibodies retain activity in such young mammalian subjects, these references are not concerned with the treatment of older mammals and do not indicate that lipase antibodies would retain their effectiveness if orally administered to healthy post-suckling mammals.

(8) While the Perryman et al and Sterling et al references do refer to the treatment of adult mammals, in those cases the mammals have their digestive processes disrupted by intestinal parasitosis. Specifically, in Perryman et al the adult scid mice are persistently infected with C. parvum which may disrupt the normal operation of the animals' digestive systems, and in the Sterling et al reference the patentees describe treating intestinal parasitosis caused by C. parvum in mammals in need of such treatment. Neither reference discloses or suggests that different antibodies, particularly antibodies having a specificity for a normally-produced enzyme (pancreatic lipase), would be able to pass through the digestive tract of a healthy adult mammal and retain enzyme-inhibiting binding capabilities.

(9) I also note that the Sterling et al reference, while mentioning the treatment of adult subjects, only offers examples of the treatment of pathological conditions in newborn mice.

(10) The Coleman patent is concerned with the treatment of diseases in ruminant animals, specifically with the use of antibodies against some of the pathogens that cause mastitis in cattle. I find nothing in the Coleman patent that would lead one skilled in the art to believe that a natural enzyme, pancreatic lipase, could be inactivated by antibodies fed orally to a healthy, post-suckling non-ruminant mammmal.

(11) Therefore, even if all of the references relied upon by the Examiner were properly combinable, which I do not agree to be the case, I would still find it surprising and unobvious from their combined teachings that the production of pancreatic lipase in a post-suckling non-ruminant mammal could be inhibited by orally feeding that mammal avian-derived pancreatic lipase antibodies.

I affirm that the statements above are true to the best of my knowledge and belief, and I am aware that any false statements herein may subject me to penalties for purjury and may jeopardize the validity of any patent or patents that may issue on the subject patent application.

Dated: March 30, 2000

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Biology of the Mammal

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into a longitudinal groove in the squamosal bone of the skull, whilst any side to side movement is obviously restricted by the quadratojugal arch of the cheek bones (see fig. 171).

We have seen in the sheep, dog and rabbit three very different sets of teeth, each designed with a jaw joint adapted to the special type of dentition. Each of these three animals is a very specialized feeder and by comparison man has a very unspecialized set of teeth. This may be related to the fact that there is little selective value for man in having specialized teeth, since he has the ability to use tools to help him in his feeding.

DIGESTION AND THE ALIMENTARY TRACT

The principle of digestion. The food ingested by the mammal contains a great variety of compounds which have been incorporated into the tissues of other animals and/or plants. Many of these compounds are highly complex, with high molecular weights and are often insoluble in water. The function of digestion is to alter the ingested food to make it available for absorption into the body, and in order to do this many of the compounds have to be broken down into simpler substances of lower molecular weight, soluble in water and capable of being absorbed through the mucous membrane of the intestine. Thus protein molecules must be broken down to their constituent amino acids before they are absorbed. Each animal species, indeed each individual, builds up its protein from constituent amino acids in a special pattern and if food proteins were absorbed directly into the blood stream they would act as antigens (see p. 567) and call forth the production of antibodies; once antibodies have been formed then continued absorption of the protein into the blood stream could lead to a fatal shock reaction. Thus apart from the physical problems of absorbing large complex protein molecules into the blood, digestion of proteins into constituent amino acids is virtually a biological necessity. Carbohydrates are stored by plants and animals in complex forms viz. starch, cellulose, glycogen, and these must be broken down into simpler substances, e.g. glucose, before absorption takes place. Even the simpler carbohydrates in the form of di-saccharides are not absorbed as such but are converted to monosaccharides. Fats are different in that some fat may be absorbed as such, in the form of very fine particles, and various digestive processes are engaged in producing such fine particles.

The complex food is broken down into simpler substances by the process of hydrolysis, in which a great variety of enzymes are engaged. Although we may describe the hydrolysis of foods as occurring in varying

stages, each stage catalyzed by a different enzyme, perhaps in different parts of the alimentary tract, it is necessary to try to view the process as a whole in which many enzymes are acting in integration to achieve the hydrolysis of the food-stuffs.

The digestive abilities of animals vary from one species to another. Herbivores for example employ special mechanisms (p. 398) for the digestion of the carbohydrate cellulose, which is such a predominant part of the structure of plants. Probably no mammal possesses an enzyme capable of hydrolyzing cellulose and they have to rely upon bacteria to do this for them. Carnivores are unable to digest cellulose, and indeed this carbohydrate does not form a part of the diet of such animals.

The alimentary tract

The alimentary tract is a long hollow muscular tube starting at the mouth and ending at the anus. Along its length are well defined regions, buccal cavity, pharynx, oesophagus, stomach, duodenum, ileum, caecum, appendix, colon and rectum. Opening into the alimentary tract are the ducts of several glands which produce secretions concerned with the digestion of food; these glands include the salivary glands, pancreas and liver. The gut is suspended from the dorsal wall of the coelomic cavity by a double layer of the peritoneum which lines the coelom, and between the two layers of peritoneum pass the blood vessels, nerves and lymphatics which supply the gut.

The basic structure of the gut is shown in transverse section in fig. 172. The innermost layer consists of the mucosa. In the buccal cavity and anal canal this consists of a layer of squamous stratified epithelium since these regions were formed in the embryo by intuckings of ectoderm. The remaining portions of the gut (except the oesophagus) are lined by a simple columnar epithelium. In some regions there are intuckings of this epithelium into the deeper layers of the wall of the gut to form glandular structures producing digestive secretions. In the small intestine the mucosal layer is highly folded to form the intestinal villi, which greatly increases the surface area available for the absorption of digested food-stuffs. Lying beneath the mucosa is a loose connective tissue, containing blood vessels and lymphatics, called the submucosa. In most regions of the gut this submucosa contains a thin layer of muscle, the muscularis mucosa.

Outside the mucosa and submucosa are the muscle layers of the gut, an outer longitudinal and an inner circular layer. These layers of muscle consist of smooth muscle fibres except in the upper part of the

The control of gastric secretion. Three phases of gastric secretion are described, the nervous, gastric and intestinal phases. The first stimulus to the production of gastric juice is a nervous one. When we see, smell or taste food, impulses pass along the vagus nerve to the stomach stimulating the production of gastric juice, and this prepares the stomach to receive the food. This was first demonstrated by Pavlov in dogs. He operated on dogs in order to bring the oesophagus out to open in the neck so that food could not pass directly into the stomach. In the same dogs he prepared pouches of stomach which were brought to the surface of the body so that specimens of gastric juice could be easily obtained. When these animals ate, the food passed out from the opening in the neck but gastric juice was still produced from the stomach. When the vagus nerves to the stomach were cut the production of gastric juice ceased.

The next phase of gastric secretion is called the gastric phase and depends upon the fact that the contact of food with the gastric mucosa stimulates the production of gastric juice. This is not a direct effect but the food causes the mucosa of the pyloric region to produce a hormone called gastrin which circulates in the blood back to the rest of the stomach which responds by the production of gastric juice. The gastric juice produced in response to gastrin appears to be predominantly acid and is not rich in pepsin.

When semi-digested food reaches the small intestine there is a further reflex production of gastric juice, perhaps based upon the production of another hormone from the mucosa of the duodenum.

DIGESTION IN THE STOMACH. There are only two known enzymes produced in the stomach, pepsin and rennin. Pepsin is secreted in the inactive form pepsinogen and activated by hydrochloric acid. Once pepsin is formed it is capable of activating more pepsinogen. Pepsin belongs to a group of protein digesting enzymes called endopeptidases (which include the enzymes trypsin and chymotrypsin produced by the pancreas). These enzymes by acting upon the peptide bonds (p. 104) within the molecules of protein break up the large protein molecules into smaller fragments. These smaller fragments are then further broken down by a group of enzymes, produced by the small intestine, called exopeptidases. These exopeptidases act by breaking down terminal peptide bonds to liberate free amino acids. The differences between pepsin, trypsin and chymotrypsin lie in the fact that each enzyme is capable of breaking down only certain peptide bonds, depending upon the chemistry of the protein molecule adjacent to the peptide bond.

In the stomach then, protein digestion is begun by the action of pepsin, which, by acting as an endo-peptidase, breaks down the

molecules of protein into smaller fragments. These smaller fragments, sometimes called polypeptides, are broken down further when they pass into the duodenum and small intestine and meet other enzymes.

There is no fat digesting enzyme produced in the stomach but the condition of the fat is altered by the warmth and churning action of the stomach. Further, globules of fat are liberated from animal tissues when these become softened and partially digested by the enzyme pepsin.

There is no enzyme produced which is capable of digesting carbohydrates, but the action of the enzyme ptyalin, which is mixed with the food, continues until the pH of the gastric juice falls sufficiently to inactivate this enzyme. Some disaccharides e.g. sucrose, are hydrolysed by the presence of dilute hydrochloric acid into monosaccharides. The special features of the stomach of some herbivores for the digestion of carbohydrates is described on p. 397.

Rennin is another proteolytic enzyme and is characteristically found in the gastric juice of young mammals. It is secreted in an inactive form, pro-rennin, which is activated by the hydrochloric acid of the gastric juice. Rennin catalyses the conversion of the protein of milk, caseinogen, into paracasein which is precipitated in the stomach as a calcium salt. The precipitated paracasein forms a firm curd in the stomach. This process ensures that milk stays for some time in the stomach so that it becomes exposed to the action of the proteolytic enzymes.

STOMACH MOVEMENTS AND EMPTYING. The contents of the stomach are mixed by waves of peristaltic contraction which pass along the stomach from cardia to pylorus. The pyloric sphincter is open for most of the time but contracts as a wave of peristalsis reaches it. Food is free to leave the stomach for the duodenum as soon as the consistency is sufficiently fluid and as soon as the peristaltic waves are strong enough to force the chyme out through the bottle neck which the pylorus represents. The rate at which the stomach empties depends upon the type of food contained. Naturally fluids tend to pass out quicker than solid foods. Fats have a characteristic effect in slowing the rate of stomach emptying and this explains why hunger does not return so quickly after a meal containing a good proportion of fat as after a light carbohydrate meal. There is also a possibility that a hormone, called enterogastrone, produced by the duodenum exerts a controlling influence on gastric motility and emptying.

The small intestine. The chyme produced by the stomach is poured into the first part of the small intestine, the duodenum. Here the digestive juices produced from the mucosa of the duodenum itself